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Investigating the biomedical applications of gold

R. HEWER, M. COYANIS, T. TRAUT, M. MPHAHLELE, J. COATES and E. VAN DER LINGEN
AuTEK Biomed, Mintek

Introduction

Transition metals have been widely used in medicine throughout history. The medicinal use of metals extends back to the earliest recorded history when the Chinese used gold as treatment for a variety of ailments. The ancient Egyptians used copper to sterilize water and mercury was reportedly used by Hippocrates in 400BC. Thereafter, numerous other metals have been used as treatment throughout the centuries. For example, zinc sulphate was used as an emetic in the 17th century and zinc oxide was used to treat epilepsy in the 18th century. This use of metals, and numerous other instances, which have been well described in Sneader 2008,[1] make for interesting reading but largely occurred prior to the advent of rigorous scientific method. Therefore, although there are exemptions, most therapeutic applications of metals prior to the modern age lack scientific grounding and have been found to be mostly ineffective. Of more relevance are metal-based medicines approved by regulatory bodies (i.e. Food and Drug Administration; FDA) that are in current use as therapeutic drugs. There are presently a large number of metal-based drugs that are approved for use by the FDA ranging from over the counter medicines, such as bismuth subsalicylate for gastrointestinal problems, to prescription drugs such as lithium carbonate for the treatment of manic depression. The list of metal-based medicines approved by the FDA not only incorporates base metals but also includes precious metals. Platinum complexes have been found to be potently active against several different types of cancers while gold complexes have shown application as treatment for rheumatoid arthritis (RA).

With the well-established foundation that exists for metal-based medicines, it is imperative to continue exploration into new therapeutic areas. The precious metals; gold, ruthenium and platinum, continue to attract scientific interest in the field of biomedicine and have been widely researched. Scientific studies conducted on gold complexes have demonstrated the potential of this metal for the treatment of HIV/AIDS, cancer and malaria. These diseases are also specific health concerns for developing nations; countries where disease has devastating impact. Within South Africa alone, an estimated 5.7 million people are infected with HIV/AIDS,[2] approximately 7 000 new cases of malaria are reported annually, and it is projected that 1 in 4 persons will develop cancer. Continuous development of therapeutic drugs to combat these diseases is therefore a priority, and the exploration of gold-based compounds for this purpose is warranted.

Notwithstanding the need for new drugs, the task of bringing a drug to market is an exceedingly challenging task. Each compound undergoes stringent assessment to ensure that only highly efficacious and safe compounds are made available for human use. As such, the development of a compound from the early stages of drug discovery—through preclinical and clinical studies—to market approval is both a lengthy and costly process. On average, the drug development process takes a median of 15 years (range 10–>18 years) with costs totalling an estimated US$800 million.[3] As a result of the time and cost implications, the compound attrition rate within the drug development pipeline is high. After initial discovery a compound has a 1 in 10 000 chance of succeeding to market while a compound that has reached clinical trials still only stands a 20% chance of approval. Although challenging to achieve, approved drugs (and particularly those that fulfil unmet needs) have shown to yield considerable returns on investment and, most notably, have significant impact in the reduction of disease-related mortality and the improvement of human health.

This paper discusses the potential beneficiation of gold in the field of medicine, highlighting specific areas within the global pharmaceutical market where gold-based compounds may find application.

The global pharmaceutical market

The global pharmaceutical market was valued at over US$ 724 billion in 2008 and is expected to grow by a further 4.5–5.5 per cent in 2009 according to IMS Health.[4] This market was dominated by US expenditure with pharmaceutical sales of US$311.8 billion in North America. It is closely followed by Europe with sales of US$ 247.5 billion in 2008. The combined market in Africa, Asia and Australia is valued at US$90.8 billion followed by Japan and Latin America with sales of US$76.6 billion and US$46.5 billion respectively.[4]

Table I depicts the top 15 drug classes of 2008. As shown, oncologics (anti-cancer agents) constitute the top selling drug class with just over 6% of the total market, with market indicators suggesting that it will remain the top selling drug class in 2009. Classified as an unmet need and with high patient treatment price per year, anti-cancer agents are set to exceed sales of US$55 billion in 2009.[4]

The top selling drug of 2008 was Lipitor (for the treatment of cholesterol) with sales of US$13,655 billion.[4] With the global pharmaceutical market forecast to grow to US$929 billion in 2012,[5] pharmaceuticals remain a vastly lucrative market.

Existing use of precious metals in medicine

Most modern medicines that incorporate a precious metal as the active ingredient are summarized below in Table II. These medicines are all currently FDA approved and are marketed in the USA and other regions. Of particular note

Table I
The top 15 drug classes as per global sales in 2008

	2008 rank	2008 sales (US$ bn)	% Growth 2008
Global market		724.465	4.4
Oncologics	1	48.189	11.3
Lipid regulators	2	33.849	-2.3
Respiratory agents	3	31.271	5.7
Antidiabetics	4	27.267	9.6
Acid pump inhibitors	5	26.525	0.6
Angiotensin II antagonists	6	22.875	12.6
Antipsychotics	7	22.853	8.0
Antidepressants	8	20.336	0.6
Anti-epileptics	9	16.912	9.7
Autoimmune agents	10	15.933	16.9
Platelet aggr. inhibitors	11	13.633	10.3
HIV antivirals	12	12.234	11.9
Erythropoietins	13	11.458	-13.9
Non-narcotic analgesics	14	11.161	3.6
Narcotic analgesics	15	10.606	8.8

This table is adapted from the IMS Health website.[4]

Table II
FDA approved medicines with a precious metal-based active ingredient

Drug Name	Active ingredient	Company	Marketing status	Dosage form; Route	Strength
Carboplatin	Carboplatin (platinum)	Bedford Labs Watson Labs Abraxis Pharm Hospira Pliva Sandoz Spectrum Pharms Teva Parental Pharmachemie Fresenius Kabi Oncol Sun Pharm Inds Generamedix Ebewe Pharma Plive Lachema Akorn	Prescription	Injectable; injection	Multiple strengths, mostly 10 mg/ml (5.25 mg Pt/ml)
Paraplatin	Carboplatin (platinum)	Bristol Myers Squibb	Prescription	Injectable; IV (infusion)	
Oxaliplatin	Oxaliplatin (platinum)	Fresenius Kabi Oncol Ebewe Pharma Hospira Worldwide Sun Pharm Inds Ltd	Prescription	Injectable; IV (infusion)	Multiple strengths, mostly 5 mg/ml (2.45 mg Pt/ml)
Eloxatin	Oxaliplatin (platinum)	Sanofi Aventis US	Prescription	Injectable; IV	
Cisplatin	Cisplatin (platinum)	Teva Parental Bedford Pharmachemie Abraxis Pharm	Prescription	Injectable; injection	1mg/ml (0.65 mg Pt/ml)
Platinol and Platinol -AQ	Cisplatin (platinum)	Bristol Myers	Prescription	Injectable; injection	
Riduara	Auranofin (gold)	Prometheus labs	Prescription	Capsule, oral	3 mg (0.87 mg Au)

is the oxaliplatin drug sold by Sanofi-Aventis under the brand name Eloxatin. This is a platinum-containing drug for the treatment of colorectal cancer. It was ranked as the 38th top selling drug in 2007 with sales of US$2.127 billion.[6] This table clearly illustrates the market and clinical relevance of precious metal-containing therapeutic drugs.

Gold-based medicinal drugs

For decades, gold salts have been utilized for the treatment of inflammatory rheumatoid arthritis. Although their exact mechanism of action is not clearly understood, gold salts decrease the inflammation of the joint lining, thereby preventing destruction of bone and cartilage. It is quite likely that the mechanism by which gold anti-rheumatic drugs modulate the immune response is multifactorial. Their therapeutic activity may be derived from an ability of gold to undergo facile ligand exchange with biological thiolates, particularly those with low pKa values, resulting in the inhibition of activity of several different enzymes.[7] Gold(I) can chelate thiol peptides with two or more cysteine residues thus affecting antigen presentation,[8] while some gold compounds can affect the cellular redox balance by inhibiting the activity of thioredoxin reductase (TrxR).[9] Other possible mechanisms of action that have been proposed (and reviewed in Fricker, 1996)[10] include the inhibition of reactive oxygen species (ROS) and the reduction of cytokines levels through the interaction with transcription-regulating proteins. Additionally, it has also

been proposed that gold's anti-arthritic activity may be due to its ability to release peptides from major histocompatibility complex-class II (MHC-II) proteins.[11]

Auranofin (marketed under the brand name Ridaura), is an orally administered drug that received FDA approval in 1985 (Table II). Auranofin was developed following the noted efficacy of the highly potent, but injectable, gold salts aurothioglucose (brand name Solganal) and aurothiomalate (brand names Myochrisine or Aurolate). Because of their ability to prevent or slow deformities of the joints, gold salts are considered and marketed as disease modifying anti-rheumatic drugs (DMARDs).

At the time, projected sale forecasts estimated the market value of gold-based drugs at US$3.3billion by 2010. However, the development of newer treatment strategies involving corticosteroids have negatively affected the market and have largely replaced gold-based therapies in RA treatments. Nonetheless, gold salts are still considered as adequate second-line drugs to be used when arthritis persists in spite of anti-inflammatory drug intervention (corticosteroids and non-steroidal anti-inflammatory drugs, NSAIDs). In such cases, gold-based drugs are used in conjunction with first-line drugs since DMARDs and anti-inflammatory drugs have distinct mechanisms of action and yield an additive effect when used together.

In addition to its therapeutic use in the treatment of rheumatoid arthritis, Auranofin has also found off-license application in the treatment of Feltys Syndrome, psoriatic arthritis and cutaneous lupus erythematosus.[12]

New areas of exploration for gold-based compounds

As described in the preceding section, gold compounds have found clinical relevance for the treatment of rheumatoid arthritis. As to date, this remains the only approved medicinal use of gold. However, substantial research has been conducted in order to define the curative value of gold and to identify other therapeutic areas for application. In particular, gold compounds have been evaluated as agents for the treatment of HIV/AIDS, cancer and malaria—diseases which represent serious health concerns for developing countries.

Several reports have detailed and described the effective anti-HIV activity of a number of different gold complexes[13-18]. In 1993, Okada and co-workers[13] described the cell-free and cell-based antiviral effect of bis (thioglucose) gold(I) (bisAuTG). While bisAuTG demonstrated inhibition of HIV-1 reverse transcriptase (RT) in cell-free assays, it is not readily taken up by cells and the cell-based activity was attributed to interaction with Cys-532 on gp120. The anti-RT mechanism of action was supported by studies in which gold (III) porphyrins were shown to inhibit the enzyme at submicromolar concentrations.[14] Traber *et al*., 1999,[15] suggested an alternative mechanism of action for gold compounds. Building on from earlier work which demonstrated that monovalent gold compounds inhibited the DNA binding of NF-K_B,[16] this group showed that auriothioglucose inhibits tumour necrosis factor alpha (TNF-α)-induced HIV-1 replication. In addition to the various in vitro studies conducted, a clinical report detailed the increase in CD4 count of an HIV/AIDS patient not accepting antiretrovials but treated for psoriatic arthritis with Auranofin.[17] These findings all provide scientific merit and support for the investigation into gold complexes for the treatment of HIV.

The evaluation of gold compounds for anti-cancer activity stems from the serendipitous discovery and subsequent success of Cisplatin. Identified in 1965, the platinum-containing Cisplatin was found to have potent effect against cancer.[19] This prompted the search for other metal-based compounds with anti-tumour properties. Numerous platinum compounds were tested and this ultimately led to the discovery and development of Carboplatin[20] and Oxaliplatin.[21] As Gold(III) is isoelectronic and isostructural with Platinum (II), it was suggested that gold compounds may also be useful candidates. As such, numerous structurally-diverse gold compounds have been prepared and evaluated for anti-cancer activity with positive outcomes.[22–32] Although the screening of Auranofin and Auranofin analogues yielded a limited spectrum of activity,[22,23] organogold(III) DAMP (DAMP = o-$C_6H_4CH_2NME_2$) complexes[24,25] and triphenylphosphine-gold (I) complexes have shown significant activity.[26,27] The work conducted on the latter compounds led to the development of bis(diphos)gold(I) complexes. These complexes had highly promising anti-tumor activity but cardiovascular toxicity pre-empted clinical trials.[28-30] In a recent study, mononuclear gold(III) complexes, organogold(III) compounds and dinuclear oxo-bridged gold(III) complexes were evaluated in several human tumor cell-lines.[31]

As seen with the treatment of rheumatoid arthritis and the inhibition of HIV-1 replication, the mechanism of anti-cancer action is not well defined. Much work, particularly in the early stages of investigation, explored the interaction of gold compounds with DNA. However, more recent studies have demonstrated that gold compounds have a distinct mechanism of action to the platinum anticancer compounds and novel targets proposed include the mitochondrial membrane, cysteine proteases (notably caspases and cathepsins) and thioredoxin reductase (as reviewed in Fricker, 2007,[32] and Gabbiani *et al*., 2007,[33]).

Nonetheless, the pronounced anti-cancer activity and good tumour selectivity described in literature demonstrate the outstanding potential of gold compounds for the treatment of cancer.

Gold complexes have additionally been tested for anti-plasmodial action to determine potential benefit in the treatment of malaria.[34-36] In early studies, the chloroquine (CQ) complex of triphenylphosphinegold(I), Au(PPh_3)-CQ showed promising activity against two different strains of *Plasmodium falciparum*.[34] A separate study demonstrated the inhibition of plasmodial activity by Auranofin in the nanomalor concentration range and by other gold compounds (AuCyclam, Au(PEt_3)Cl and aurothiomalate) to be in the micromolar range.[35] The anti-plasmodial action of gold complexes may be a consequence of metal-induced oxidative stress or due to its interaction with TrxR or falcipain.[36] These findings merit further investigations into the potential of gold complexes as anti-malarial agents.

Through partnership with Harmony Gold Mining Company and through an extensive collaboration network, AuTEK Biomed aims to contribute to investigations into gold-based therapeutics. Research undertaken to date by AuTEK has examined the solubility, stability, cellular uptake, cytotoxicity, anti-HIV activity, anti-cancer activity, anti-malarial activity and overall drug-likeness of gold-based compounds. The findings from these studies largely support previous findings and validate further research into the potential of gold-based therapeutics.

Conclusion

The pharmaceutical market remains vastly lucrative with high returns on investments into successful drugs. Drugs fulfilling unmet needs are highly attractive and of particular importance. Numerous transition metals, including precious metals, have been developed into FDA-approved and clinically available drugs. Of note is the successful platinum-containing drug oxaliplatin (Eloxatin). Gold-based therapeutics have found success in the treatment of rheumatoid arthritis, even though more potent drugs have mostly replaced gold therapy. Current investigations by numerous investigators including AuTEK Biomed have explored and continue to explore the possibility of developing gold-based complexes for use in the treatment of cancer, HIV and malaria. Both cancer and HIV rank within the top 15 drug classes in terms of sales and both are classified as having unmet needs in terms of therapy. The successful development of gold-based drugs within these disease areas would be a profitable and positive beneficiation for gold.

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Raymond Hewer

AuTEK Biomed, Mintek

Raymond Hewer joined Mintek in 2006 after completing his PhD in Biochemistry at the University of Johannesburg. His PhD focused on the development of HIV vaccine components. Raymond works within AuTEK Biomed, a multidisciplinary group involved in the field of early-stage drug discovery. His primary interest is the identification of novel compounds with promising antiviral activity. He has published several articles and has presented his work both locally and abroad.

Judy Coates

Head: Biomed, Mintek Biomed, South Africa

Judy joined Mintek in 2003 after obtaining her PhD in Organic Chemistry at the University of Johannesburg (Rand Afrikaans University). She began her research career looking at the synthesis and biological activity of a variety of phosphine compounds in a secondment to University of Witwatersrand. This research has since resulted in the filing of a South African Patent. In 2004 Judy undertook a research visit to Heidelberg, Germany, where she investigated the gold labelling of neurologically active pentapeptides. Shortly after her return to South Africa she began heading up the AuTEK Biomedical Programme, along with taking on an honorary position at the University of Witwatersrand. Over the past six years Judy has actively supervised and co-supervised student projects at collaborating universities, along with the research activities at Mintek, where she is now involved in the development of metal-based therapies for HIV, cancer, and malari